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Letter to the editor

HLA and PF4 antibody production after adenoviral vector SARS-CoV-2 vaccination

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Keywords

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To the Editor,

Vaccine-induced thrombotic thrombocytopenia (VITT) is a rare and devastating disease resulting from platelet activation and aggregation following the first injection of SARS-CoV-2 vaccines (e.g. Ad26.COV2.S and ChAdOx1 nCoV-19). This condition leads to accelerate thrombin generation that is caused by antigen-antibody complexes consisting of platelet factor 4 (PF4), polyanion (P), and IgG anti-PF4/P-reactive antibodies. It is as yet unclear why only a subset of individuals produce IgG-specific anti-PF4/P antibodies after adenoviral vector SARS-CoV-2 vaccination[1]and a smaller subset of patients produce high levels (optical density ≥1.20) of pathogenic anti-PF4/P antibodies[2-4]that can cause platelet activation. The basis of this heterogeneity in antibody development is not yet worked out but is likely due to genetic variation (e.g. class II human leukocyte antigen (HLA-II)). Here we describe the potential role of HLA-II in VITT antibody production.

HLA-II molecules classically bind peptides derived from exogenous proteins (both self and foreign) and present them for recognition by CD4+ helper T lymphocytes (Th) which play an important role in the production of autoantibodies. The B cell response is presumably elicited by exposure to a cryptic antigen when P and PF4 are bound. It can occur via two pathways, thymus-dependent (TD) and thymus-independent (TI) pathway (Figure 1).

Patients with VITT have some features of a TD pathway in that they rapidly produce high levels PF4/P-reactive antibodies of the IgG Isotype, indicating previous contact with PF4/polyanionic macromolecules throughout one's lifetime and inappropriate Th cells activation. In this case, it appears that inappropriate expression of HLA-II/peptide complex

can sensitize autoreactive Th cells and the likelihood of developing thrombocytopenia and thrombosis by several potential immunological mechanisms.

First, it presumes that PF4/P complex acts as a self-antigen or endogenous antigen that could select autoreactive Th cells or fail to select the FOXP3+ regulatory T cells through an aberrant antigen presentation by HLA-II molecules. Moreover, the knowledge that inflammatory stimulus may activate preexisting, inactive PF4/heparin-specific B lymphocytes by B-cell tolerance breakdown in autoimmune heparin-induced thrombocytopenia (aHIT)[5], suggests that similar events are likely to occur in VITT and thus increasing concentrations of PF4/P auto-antibodies in susceptible individuals. In favor of this hypothesis is the rapid generation of pathologic IgG PF4/P autoantibodies that shared biologic and clinical characteristics of aHIT antibodies, including preferential binding to PF4 site[6]and causing thrombocytopenia and thrombosis in younger-usually females-subjects, a population which is most susceptible to autoimmunity. Furthermore, low-titer non-pathologic IgG antibodies without manifesting thrombocytopenia or thrombosis are present in healthcare workers [1, 7], suggesting that some people may already be sensitized and have a breakdown of tolerance.

Second, polymorphism in HLA alleles or haplotypes could modulate anti-PF4/P hyperresponsiveness. Previous studies have implicated HLA-DRB1*03:01 and -DQB1*02:01 with the formation of high levels PF4/heparin antibodies and HIT [8]. It appears that variations in the amino acids encoded by these polymorphic alleles may present PF4/P neo-peptides that preferentially induce TD response, resulting in excessive production of class-switched high-affinity VITT antibodies. For this to occur, the follicular B cells need to make a cognate interaction with Th cell, which is crucial in determining the differentiation of naive B cell into high-affinity plasma cells and in regulating B-cell stimulation versus tolerance.

Third, PF4/P antigen can bind to the HLA-binding cleft and, altering the specificity of peptide binding, change the repertoire of self-epitopes presented. This results in the presentation of neo-self-peptides capable to activate Th cells, resulting in production of VITT IgG antibodies with primary exposure to PF4/polyanion.

Finally, variation in binding groves of associated DR/DQ molecules could influence not only quantitative anti-PF4/P production but also the pathogenic capacity of induced VITT. Tølbøll Sørensen AL et al reported a severe case of multiple thromboses due to adenoviral vector Covid-19 vaccine [9]. The HLA-II type was DRB1*01/DRB1*11; DQB1*03:01/DQB1*05; and DPB1*02:01/DPB1*04:01, suggesting that HLA-DRB1*11 and -DQB1*03:01 could be a poor prognosis of VITT. In another research, DRB1*11 is tightly linked to DRB3*01:01

allele, identified as a potential immune factors for the generation of anti-platelet autoantibody and HIT [10].

Unlike TD pathogenic model of VITT, PF4/P may generate ultra-large complexes (ULCs) [11] that can crosslink multiple specific B cell receptors (BCR) on marginal zone B cells. This high-valency antigen may also activate the complement [9] and bind complements activation components. This process, is thought to stimulate rapid production of IgG anti-PF4/P antibodies by marginal zone B lymphocytes independent of HLA-II restricted-T-cell help.

By combining these two pathways, some patients mount an unusual B cell response that enables the host to rapidly produce IgG PF4/P antibodies that can be secreted at a sufficient rate to accelerate platelet activation and aggregation, thereby triggering the development of thrombopenia and thrombosis. A priori identification of patients with high-risk HLA susceptibility alleles (or haplotypes) could make prevention of severe VITT disease possible.

Conflict of interest

The authors declare that they have no conflict of interest.

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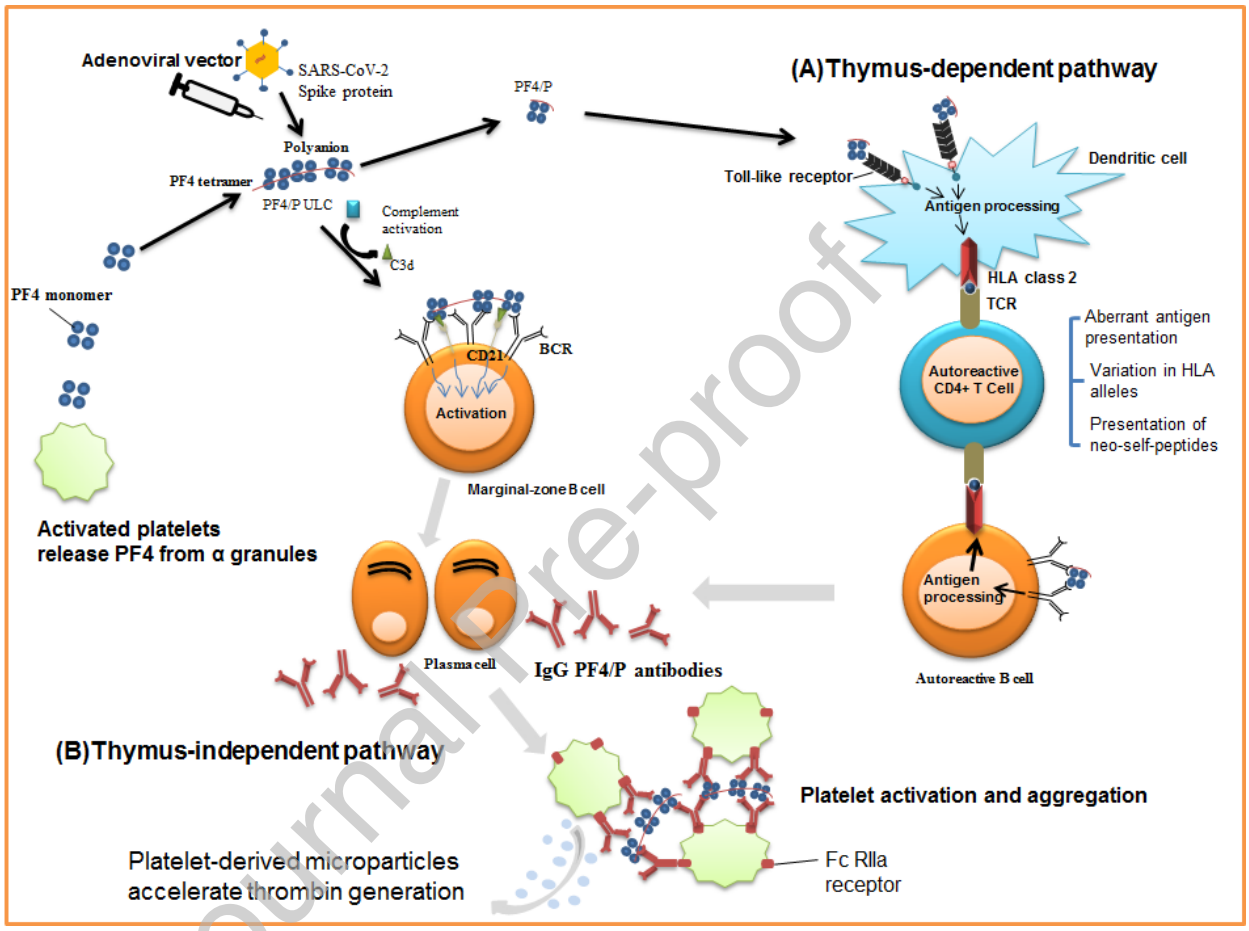

Figure 1. Features of B cell responses in VITT

(A) In VITT- associated HLA-II-restricted T cell help, PF4/polyanion complexes may activate preexisting, inactive PF4/P-specific B lymphocytes by B-cell tolerance breakdown. These autoreactive B cells may produce high levels of anti-PF4/P IgG antibodies with first exposure to SARS-CoV-2 vaccines. (B) Ultra-large complexes (ULCs) of PF4 may potentiate rapid production of IgG anti-PF4/P antibodies by marginal zone B cells independent of HLA-II restricted-T-cell help.